

Defining the Human Envirome An Omics Approach for Assessing the Environmental Risk of Cardiovascular Disease

Daniel W. Riggs, Ray A. Yeager, Aruni Bhatnagar

Abstract: Both genetic and environmental factors contribute to the development of cardiovascular disease, but in comparison with genetics, environmental factors have received less attention. Evaluation of environmental determinants of cardiovascular disease is limited by the lack of comprehensive omics approaches for integrating multiple environmental exposures. Hence, to understand the effects of the environment as a whole (envirome), it is important to delineate specific domains of the environment and to assess how, individually and collectively; these domains affect cardiovascular health. In this review, we present a hierarchical model of the envirome; defined by 3 consecutively nested domains, consisting of natural, social, and personal environments. Extensive evidence suggests that features of the natural environment such as sunlight, altitude, diurnal rhythms, vegetation, and biodiversity affect cardiovascular health. However, the effects of the natural environment are moderated by the social environment comprised of built environments, agricultural and industrial activities, pollutants and contaminants, as well as culture, economic activities, and social networks that affect health by influencing access to healthcare, social cohesion, and socioeconomic status. From resources available within society, individuals create personal environments, characterized by private income, wealth and education, and populated by behavioral and lifestyle choices relating to nutrition, physical activity, sleep, the use of recreational drugs, and smoking. An understanding of the interactions between different domains of the envirome and their integrated effects on cardiovascular health could lead to the development of new prevention strategies and deeper insights into etiologic processes that contribute to cardiovascular disease risk and susceptibility. (*Circ Res.* 2018;122:1259-1275. DOI: 10.1161/CIRCRESAHA.117.311230.)

Key Words: air pollution ■ coronary artery disease ■ diet ■ exercise ■ smoking prevention

Animals are divided into: (a) belonging to the Emperor, (b) embalmed, (c) tame, (d) suckling pigs, (e) sirens, (f) fabulous, (g) stray dogs, (h) included in the present classification, (i) frenzied, (j) innumerable, (k) drawn with a very fine camelhair brush, (l) et cetera, (m) having just broken the water pitcher, and (n) that from a long way off look like flies.

—The Celestial Emporium of Benevolent Knowledge

Cardiovascular disease (CVD) results from complex, but poorly understood, interactions between genetic and environmental factors. Although some forms of CVD such as familial hypercholesterolemia, hypertrophic cardiomyopathy, and long QT and Brugada syndromes are clearly heritable forms of CVD, the most common cause of CVD—atherosclerotic disease—is not attributable to genetic predisposition. Atherosclerosis is the leading cause of death worldwide¹; and because of its high prevalence, it cannot be entirely attributed to the presence of rare high penetrance susceptibility genes that

impart disease risk to only a few individuals. Moreover, even within a genetically stable population, the risk of CVD because of atherosclerosis could be modified by changing the environment. For instance, immigration of South East Asian to the United Kingdom² or the Japanese to the United States,³ results in a 2- to 3-fold increase in their risk of myocardial infarction and stroke. Even within the same geographic location, a change in the social environment could affect CVD risk. For instance, between 1971 and 1995, CVD rates in Finland plummeted by 75% because of the implementation of national nutritional and antismoking programs.⁴ Likewise, in the last few decades in the United States and the United Kingdom, CVD mortality has decreased by 45% to 60% largely because of societal changes.^{5,6} In contrast, coincident with industrialization and Westernization, CVD mortality in men living in Beijing has increased by 50% within 15 years.⁷ Clearly, changes in the social environment can significantly modify CVD risk, independent of genetic factors.

Further evidence supporting the environmental nature of CVD risk comes from many studies showing that the risk of

From the Diabetes and Obesity Center (D.W.R., R.A.Y., A.B.) and Institute of Molecular Cardiology (A.B.), University of Louisville, KY.

This manuscript was sent to Buddhadeb Dawn, Consulting Editor, for review by expert referees, editorial decision, and final disposition.

The online-only Data Supplement is available with this article at <http://circres.ahajournals.org/lookup/suppl/doi:10.1161/CIRCRESAHA.117.311230/-DC1>.

Correspondence to Aruni Bhatnagar, PhD, Division of Cardiovascular Medicine, 580 S Preston St, Baxter II, Room 421 EF, University of Louisville, Louisville, KY 40202. E-mail aruni@louisville.edu

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Circulation Research is available at <http://circres.ahajournals.org>

DOI: 10.1161/CIRCRESAHA.117.311230

Nonstandard Abbreviations and Acronyms

CHD	coronary heart disease
CVD	cardiovascular disease
EWAS	Environment-Wide Association Studies
GWAS	Genome-Wide Association Studies
HDL	high-density lipoprotein
PM	particulate matter
SES	socioeconomic status

CVD is exacerbated by exposure to environmental pollutants, chemicals, and toxicants.⁸ Indeed, globally more individuals exposed to adverse environments die from CVD than cancer or respiratory diseases combined,⁹ suggesting that cardiovascular health is exquisitely sensitive to adverse environmental exposures and that much of the burden of CVD is acquired from living in unconducive, polluted, and unhealthy environments. Additional support for a nongenetic view of CVD comes from a variety of large cohort studies which show that as much as 80% to 90% of the disease is preventable and that individuals who maintain a healthy lifestyle have a much lower risk of CVD.^{10,11} In this regard, the nongenetic nature of CVD is similar to that of other chronic diseases, such as cancer. Analysis of the Family Cancer Database on 10.2 million individuals suggests that except for prostate and breast cancer, the risk of most other cancers attributable to familial or genetic factors is between 1% to 3%,¹² and to date most gene variants, identified by >400 GWAS (Genome-Wide Association Studies), account for only small increments in the risk of chronic diseases.¹³ Therefore to understand the causes of CVD, and to develop effective intervention and prevention strategies, it is important to evaluate and assess the effects of the environment on cardiovascular health and disease risk.

Currently, many environmental factors are not taken into account when estimating CVD risk. Most CVD estimates in use are based on multivariable regression equations in which major risk factors—total cholesterol, HDL (high-density lipoprotein), systolic blood pressure, smoking status, and diabetes mellitus—are weighted to calculate a composite risk score, which is then converted to an absolute probability of developing coronary heart disease (CHD) within a certain time frame.¹⁴ Such risk factor estimates account for 85% of the excessive risk of CHD, and the addition of other risk factors does not increase their predictive efficacy. As a result, risk factor management has become the foundation of current preventive strategies. However, such calculations provide estimates for populations, not individuals, therefore, estimates of individual risk remain probabilistic, and many cardiovascular events occur in individuals with low to intermediate risk profile.^{14,15} Clearly, better risk estimates are needed. Given that the environment seems to play a key role in developing CVD, it may be possible to improve risk prediction by assessing and including unknown environmental factors. Thus, elucidation of environmental influences may allow previously unknown input functions that may not only increase the predictability of population-level risk estimates but also provide better assessments of individual-level risk by environmental, rather than genetic, profiling.

The nongenetic, environmental nature of CVD is further reflected by the close association between CVD risk

and individual lifestyle choices. Individuals who adhere to a healthy lifestyle, maintain a healthy weight and diet, and engage in moderate physical activity and consume moderate amounts of alcohol have a much lower CVD risk than those who cannot or do not maintain a healthy lifestyle. Lifestyle risk factors account for as much as 80% of CHD events and 90% of the new cases of diabetes mellitus. However, few individuals can maintain an optimal risk factor profile and managing risk factors could be challenging. For instance in the United States, <1% of children and adults have a healthy diet pattern, and <1% children and virtually 0% adults meet all 7 (smoking, body mass index, physical activity, healthy diet, total cholesterol, blood pressure, and diabetes mellitus) criteria for ideal cardiovascular health.¹ Although there are many reasons why most individuals do not maintain a healthy lifestyle, some of these may relate to environmental influences that prevent healthy lifestyle choices. Lifestyle choices such as physical activity, healthy nutrition, and smoking are not entirely individual choices but are shaped by a wider social context. For instance, even though physical exercise is an individual choice, it is in part determined by the built environment.¹⁶ Likewise, nutritional choices are affected by the availability of fresh foods as well as complex networks of food production and distribution. Indeed, many individual lifestyle choices are shaped by marketing or propaganda, suggesting that social and economic forces in part influence choices that affect health.^{17,18} Hence, to identify and evaluate the factors that influence lifestyle choices and thereby CVD risk, we have to look beyond individual lifestyle choices and risk factor management. We have to examine the forces that influence such choices; we have to evaluate how environmental exposures affect blood pressure, insulin resistance, and dyslipidemia; and we have to investigate how novel risk factors such as circadian misalignment or sunlight exposure affect cardiovascular health. In short, we have to examine the environments in which humans live.

Defining the human environment is difficult. Humans live in complex environments; fashioned by unique combinations of culture and history, and in different geographic domains to which they have variably adapted during the course of their evolution. Past attempts to understand and quantify environmental determinants of health were thwarted by the lack of a universally accepted conceptual framework for defining the human environment, as well as the uncertain feasibility of assessing variable, multifaceted environmental factors that affect human health and disease susceptibility. Yet, as recent advances in omics approaches in biology have shown, important insights could be garnered by adopting a systems approach. Such evaluations, even if incomplete, can provide new perspectives, often missed by narrow reductionist approaches. This may be particularly true when assessing the health impact of the many interrelated and interdependent components of the environment, each of which can affect health individually and collectively. Therefore, clear definitions of the environment and its specific domains are needed to develop a conceptual framework for understanding how environmental factors affect human health, and how the contribution of different features of the environment could be evaluated using an omics approach.

Current approaches for studying the environment to date are based on either the psychosocial model or the social determinants of health. However, these models are limited by their exclusive focus on psychological or social domains of the environment. The psychological state is internal to an individual, and even though affected by the environment, it cannot be considered an environmental factor, which by definition is external to an individual. Moreover, social determinants of health do not include the natural (ecological and geographic) aspects of the human environment and do not account for personal micro-environments, which often differ among individuals living under the same societal conditions. In addition, such models rely heavily on studying each exposure separately, which precludes collective evaluation of different interacting domains of the environment. In contrast, the recently formulated exposome concept succeeds in drawing attention to the holistic nature of environmental influences, and in highlighting current deficiencies in reductionist approaches to environmental epidemiology.

Concept of the Exposome

The exposome, as defined by Wild,¹⁹ encompasses life course environmental exposures (including lifestyle factors) from prenatal period onwards. Under the exposome framework, the totality of environmental exposures comprise the inherent features of exposures and their change over time. In this view, the exposome represents the totality of exposure from conception to death, as a quantity of critical interest in understanding the environmental causes of chronic diseases. The concept of the exposome is analogous to the concept of the genome and was developed with the goal of quantifying environmental exposures with the same precision and accuracy as the human genome. However, environmental exposures are more variable than individual genomes. Unlike genomes, which are composed of the same chemical entity (DNA), environmental exposures (including, chemical exposure, social determinants of health, and lifestyle factors) belong to distinct categories that cannot be readily grouped together. All genes are comprised of DNA and, therefore, ontologically homogenous. They could be analyzed using the same methodological procedures and understood using the same conceptual categories. Other omics approaches in biology—proteomics, lipidomics, and metabolomics, have succeeded for the same reason—because they study substances of the same category (proteins, lipids, and metabolites). Such bio-omics approaches derive additional clarity by being organ-specific. For instance, proteomics of liver could not be merged with proteomics of the kidney or metabolomics of the heart. Thus, grouping all environmental factors into one amorphous set would pose difficulties similar to those that arise from simultaneously studying all biomolecules (protein, lipids, metabolites, and carbohydrates), without first distinguishing between them on the basis of their biologically distinct nature or tissue of origin. On the larger scale, this would be akin to studying plant and animal kingdoms as a whole, without first categorizing them into phyla, families, genera, and species. Hence, to redeem the promise of the bio-omics approach, we need to distinguish between different domains and components of the environment and determine how they relate to each other.

Another reason why bio-omics approaches have succeeded is that they are based on substantial knowledge of biological

pathways that link specific metabolites, proteins, and genes to other members of their class and to members of other classes. This knowledge has led to the development of clearly formulated gene ontologies that assign molecular activity to gene products, locate where the genes are active, and identify which biological processes specific genes control. Similar ontologies have been developed for proteins and metabolites. Metabolic pathways have been mapped in exquisite detail, and the relationships between several enzymes and metabolites are well-known. Although by no means complete, this knowledge does provide a clear ontological foundation for omics research, so that when new components are discovered, there is little uncertainty whether they are proteins, genes, or metabolites, and how they may be related to known families of biomolecules. Similarly, when new relationships are found, there is sufficient background knowledge to assign appropriate hierarchies and domains within existing frameworks of biological knowledge. As an example, even though not all the elements were discovered, the periodic table provided an ontological basis for assigning newly discovered elements to specific groups and indeed, to identify new elements predicted solely on the basis of expected ontological relationships. However, no such ontology has been developed for environmental factors, and therefore, it may be premature to enumerate components of the environment or to quantify their influence on health. Hence, extensive ontological and taxonomic work is needed to lay the foundation for constructing inclusive models of the environment for the purpose of studying its health effects using omics approaches.

The exposome model of the environment includes 3 different categories of environmental exposures: internal, specific external, and general external.^{20,21} The internal environment is thought of as the body's internal chemical environment, in which the exposures are biologically active chemicals within the body and consist of chemicals produced by metabolism, physical activity, gut microflora, inflammation, and oxidative stress. Specific external exposures consist of environmental pollutants, infectious agents, diet, alcohol, and tobacco smoke. Last, general external exposures in the exposome include socioeconomic status (SES), psychological influences, built environment, and climate. Although assessing exposure by measuring the internal chemical environment is attractive and bioactivation of a toxicant could be considered to be a part of exposure, tissue levels of the metabolites of external and internal chemicals, or even the levels of untransformed chemicals, reflect not only the extent of exposure, but also the rate of tissue deposition, removal, and metabolism; processes that depend on an individual's genetics, age, nutritional status, and coexposure to other pollutants. In other words, the internal chemical environment is only indirectly reflective of actual exposure, and assessing the internal chemical environment exclusively may lead to significant exposure misclassification. Moreover, internal correspondence is difficult to establish for nonchemical exposures such as SES, social networks, or built environments. In addition, studying changes in oxidative stress, inflammation, and cytokines, etc, confuses effects with causes. Changes in the production of reactive oxygen species or cytokines are responses to external exposures, not the exposure itself. Yes, we can learn much about the nature of exposure by studying its effects, but to avoid equivocation

between cause and effect, it may be important to distinguish environmental exposures from their biological consequences, and not to blur the distinction between them. It is equally important to distinguish between direct and indirect interactions between biological processes and the environment. Contrary to the common allusions to gene-environment interactions (G×E), genes and environment often do not interact directly. In some cases, the environment can directly affect genes—for example, by causing gene mutations, but in majority cases, genes synthesize proteins, which in turn synthesize lipids, carbohydrates, metabolites, and other proteins, products that respond to changes in the environment and convey this information to genes. Even epigenetic changes associated with chromatin remodeling and DNA repair mechanisms are orchestrated by proteins. Each step of these interactions is regulated by different processes and subject to different constraints that cannot be overlooked in assessing how environmental exposures affect a biological process. Hence, it is important not to equate environmental exposures to specific changes in only one class of biomolecules, that is, genes, without considering the entire biological response.

Human Envirome

In biology, the environment is defined as the totality of surrounding conditions, including the complex of physical, chemical, and biotic factors that determine form and survival of an organism or an ecological community. For humans, the environment encompasses all social, economic, and cultural conditions that affect the nature of an individual within society and could mean anything external to an individual. Although broad, this definition rules out internal processes and factors, such as organ function, or metabolic and psychological processes. It also rules out internal components, such as the gut microbiota or inhaled air, both of which, while in frequent contact with the external environment, are internal to an individual as they are modified or altered by internal processes. Analogous to the human genome, the environment could be thought of holistically as the human envirome, distinct from an internal biological process that collectively represents the interome. Nonetheless, even with such demarcation, the definition has limited utility, as it is too broad and amorphous to yield to empirical inquiry and quantitative assessment. Hence, to understand the

environment, we would have to classify it further into more tangible and categorically-differentiated domains.

As described recently,⁹ 1-way of understanding the totality of the human environment is to differentiate it into hierarchical domains of natural, social, and personal environments (Figure 1). Of these, the natural environment is the most primordial, as it encompasses and predates humans. Nested within the natural environment are social environments that arise from cultivated modes of human interaction with nature. Each domain of the environment consists of physical objects, such as living and nonliving things (plants, houses, cars), as well as relationships, such as the relationship of an individual with society or with other individuals within a social network.

To assess the health impact of the environment, we have to consider both—the objects in the environment as well as the relationships between them. However, environmental objects and relationships change over time. Because chronic diseases such as CVD have a long latency period, a life course approach is essential. This approach is critical for assessing how exposures at different life stages affect disease risk; whether over time, the effects of exposures are simply additive or progressive; how exposures at one time affect later risk trajectories; and whether the effects of early exposure are mitigated by later life adaptation. Life course approaches may also uncover critical periods when an otherwise innocuous exposure has adverse or protective effects on development and subsequent disease outcome, and distinguish them from sensitive periods when exposure has a stronger effect on disease risk than it would at other times.²² Life course approaches can also identify environmental clustering of risk (such as that because of low SES or childhood adversity) located within specific domains of the environment. In broad terms, the life course approaches are consistent with the ontological view of humans as 4-dimensional objects that unfold and develop over time. Understood this way, the envirome model could offer a useful conceptual framework for evaluating the contribution of each environmental domain to human health over time. The major domains of the envirome are as follows.

Natural Environment

The natural domain of the human environment encompasses all living and nonliving things that are natural (ie, not man-made).



Figure 1. Model of the human envirome. The entirety of the human environment could be differentiated into natural, social, and personal domains. Each domain is nested within another. The natural environment is the most primordial. The social environment is nested within the natural environment, as it is derived from and developed within nature. Personal environments are constructed from elements from the social and natural environments by individual choices or happenstance. Although each domain is categorically distinct, their boundaries are porous. The natural environment permeates through both social and personal domains, and often the construction of social and personal environments affects the natural environment. Each domain individually and collectively affects cardiovascular health, and moderates, modifies, or rectifies the influence of other domains. (Illustration credit: Ben Smith.)

It includes the subdomains of the geosphere and the biosphere (Figure 2), both of which significantly affect cardiovascular health.

Geosphere

The geosphere of an individual is characterized by its location, which could be described in terms of longitude, latitude, and altitude. Components of the geosphere differ in their climate, levels of sunlight, temperature, rainfall, and seasons. An individual's geosphere is characterized by local geography, geology, and terrain, particular to that individual as well as more universal features such as diurnal cycles of night and day, and in most places, a cyclic change in seasons. The geosphere is studied broadly within the sciences of biology, ecology, geography, and meteorology, but its relationship to cardiovascular health has received less attention. Nevertheless, there is evidence to support the view that the geosphere significantly influences CVD risk.⁹ Natural forces such as changes in local geography, floods, and sea temperatures have been important in the development or dissolution of human cultures, as well as human settlements and migrations. Even in modern societies, the geosphere continues to exert a dominant influence on human health and well-being. And, like all other living things, humans are entrained to daily cycles of night and day. A mismatch between circadian rhythms and the diurnal cycle leads to a heightened risk of CVD,²³ diabetes mellitus,^{24,25} and obesity.^{24,25} Features of geography also determine CVD risk: individuals living at high altitudes display lower rates of CVD and lower CVD risk burden than those living near sea levels.^{26–28} People who are born at a higher altitude maintain a lower CVD risk even after migrating to low altitudes later in life, suggesting that exposure to high altitude during critical periods

in early life could irrevocably decrease CHD risk and mortality.²⁷ CVD risk is affected by latitude as well. Human populations living close to the equator report lower blood pressure than those living nearer to the poles,²⁹ which may be because of differences in sunlight exposure. Humans, like plants, require adequate sunlight for photosynthesis, particularly for the generation of vitamin D. Inadequate sunlight exposure and low vitamin D levels are associated with increased CVD risk.³⁰ Even in children, low vitamin D levels have been found to be associated with increased carotid intima-media thickness in adulthood,³¹ and low neonatal vitamin D levels predict the risk of being overweight as adults.³² Variations in cardiovascular mortality with seasons and temperature^{33–36} further underscore the link between CVD and the natural environment. For instance, the likelihood of adverse cardiovascular events is higher in winter, and more CVD deaths occur in winter than in summer.³⁵ The geosphere could also be a source of pollution. Exposure to high levels of particulate matter (PM) or toxic gases, volcanoes, sand, and dust, as well as emission from plants and forest fires in the geosphere could significantly elevate the risk of both CVD and diabetes mellitus.

Biosphere

The biosphere consists of all plants, animals, and microbes. It has played a critical role in human evolution, both as a source of food as well as predators, pests, and parasites. Throughout recorded history, viral and bacterial infections have exerted a dominant influence on human survival and lifespan, and they continue to exert an important influence on public health in many parts of the world today. The biosphere also exerts an important influence on the risk of noncommunicable disease associated with

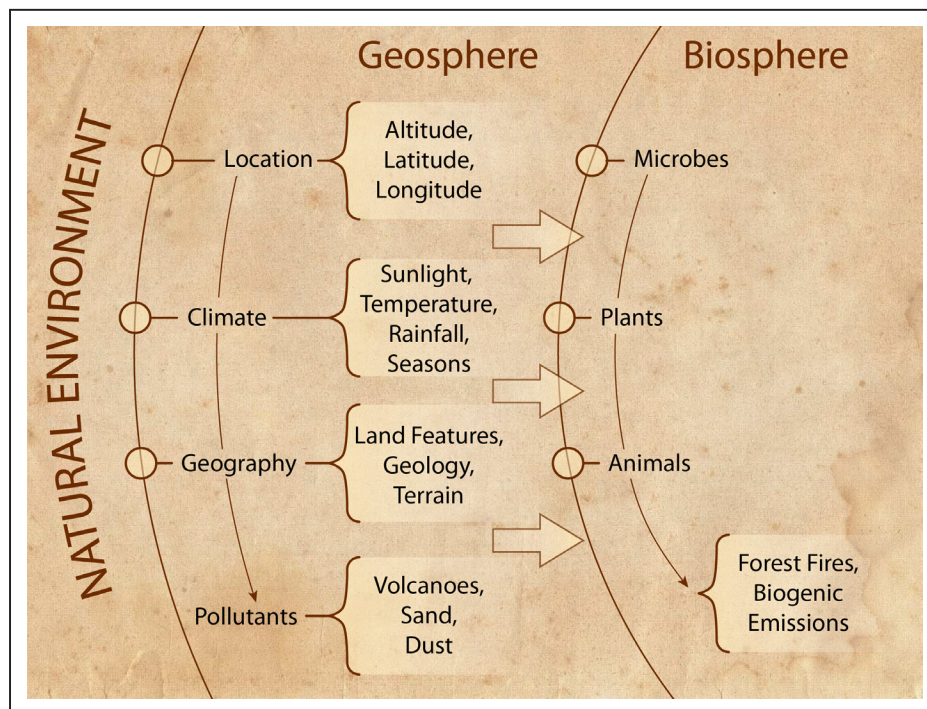
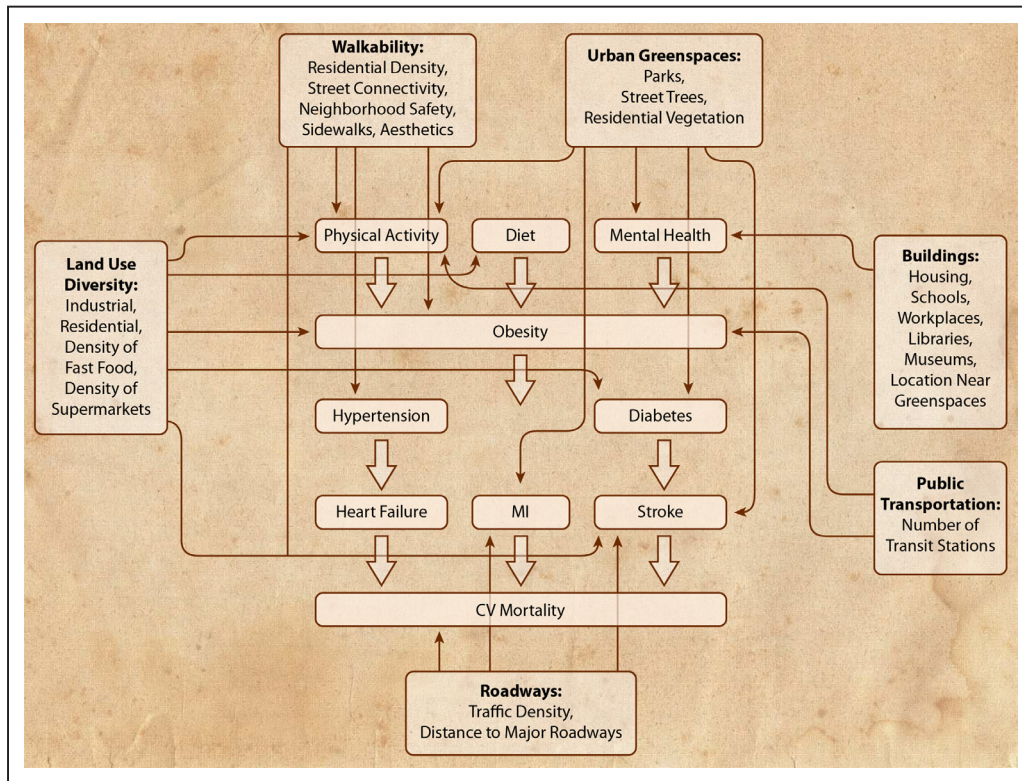


Figure 2. The natural environment. The natural environment is comprised of a geosphere and a biosphere. The geosphere is a composite of the lithosphere, hydrosphere, and atmosphere. It is characterized by its location, climate, and geography. The biosphere includes living plants, animals, and microbes. Features of the geosphere, such as altitude, sunlight, diurnal, and seasonal cycles of the earth influence cardiovascular function and are important determinants of cardiovascular health. Similarly, surrounding biodiversity and exposure to plants, animals, and microbes could result in disease as well as immune adaptation. Elements of both the geosphere and biosphere could be sources of pollution. (Illustration credit: Ben Smith.)



Scheme. Influence of built environment of cardiovascular health and disease risk. Features of the built environment affect cardiovascular disease (CVD) risk factors, cardiovascular events, and cardiovascular mortality. The diversity of land use within neighborhoods affects physical activity and food choices of residents and their risk of obesity, type 2 diabetes (T2D), or stroke. Characteristic of urban environments that affect walkability influence physical activity, and the risk of obesity, hypertension, and T2D. Urban greenspaces have been found to promote physical activity and better mental health and have been linked to a decreased risk of diabetes mellitus, cardiovascular, and stroke mortality. Features of the building used for residential and commercial purposes affect individual mental health and stress, whereas higher levels of public transportation have been linked with lower levels of obesity. Residential proximity to major roadways is associated with increased cardiovascular mortality, the risk of myocardial infarction (MI), and stroke. (Illustration credit: Ben Smith.)

chronic inflammation. Recent work has shown that high biodiversity in surrounding areas educates the human immune system. Communities of environmental microorganisms overlap and interact with human commensal microbiota; contribute to human microbial diversity, and play important beneficial immunomodulatory roles.³⁷ Hence, environments rich in microbial biodiversity confer protection against allergic and autoimmune diseases.³⁸ This concept has been extended to plant, animal,³⁷ and landscape³⁹ biodiversity as well, and is supported by studies showing an association between prevalence of good health and land cover diversity, density or bird species richness (an indicator of local biodiversity).⁴⁰ Similar associations have been reported between land biodiversity and respiratory health.⁴¹ Exposure to plants benefits human health as well. The rates of both all-cause and cardiovascular mortality are lower among populations living in areas of high greenness,^{42,43} and residential proximity to greenspaces is associated with lower levels of diabetes mellitus, stroke, and CVD,⁴⁴ and higher rates of survival after stroke (Scheme).⁴⁵

Even though the geosphere and the biosphere influence human health, humans, in turn, affect the natural environment, and this interaction could further modify the effects of the environment on humans. Extensive work has shown that global changes in land use, because of the acquisition of natural resources for human needs, has increased emissions of greenhouse gases, leading to global climate change, loss of biodiversity, and increased nutrient

inputs to the biosphere.⁴⁶ The World Health Organization estimates that between the years 2030 and 2050 climate change could cause ≈250 000 additional deaths per year. Loss of biodiversity is also an important global change in its own right.⁴⁷ Biodiversity changes affect multiple ecosystem services that have direct influences on human health, such as the availability of food, fresh water, and fuel, as well as indirect influences through changes in patterns of livelihood, income, and migration. How anthropomorphic changes in the geosphere and biosphere affect cardiovascular health remains unclear but requires urgent investigation.

Social Environment

Within the natural environment, humans create distinct and diverse social environments (Figure 3). These environments are not independent of nature but arise from the cultivation and modification of natural elements presumably for promoting human flourishing and well-being. The social environment is the collective mode by which humans organize their relationship to nature and to one another. Interactions of humans with nature result in activities such as agriculture and the development of the built environment, whereas interactions among humans result in the formation of complex and variable social networks. Such interactions generate knowledge, which accumulated and transmitted across generations, gives rise to culture, history, and economic activities, as well as technology, health services, agricultural practices, and networks of food transport

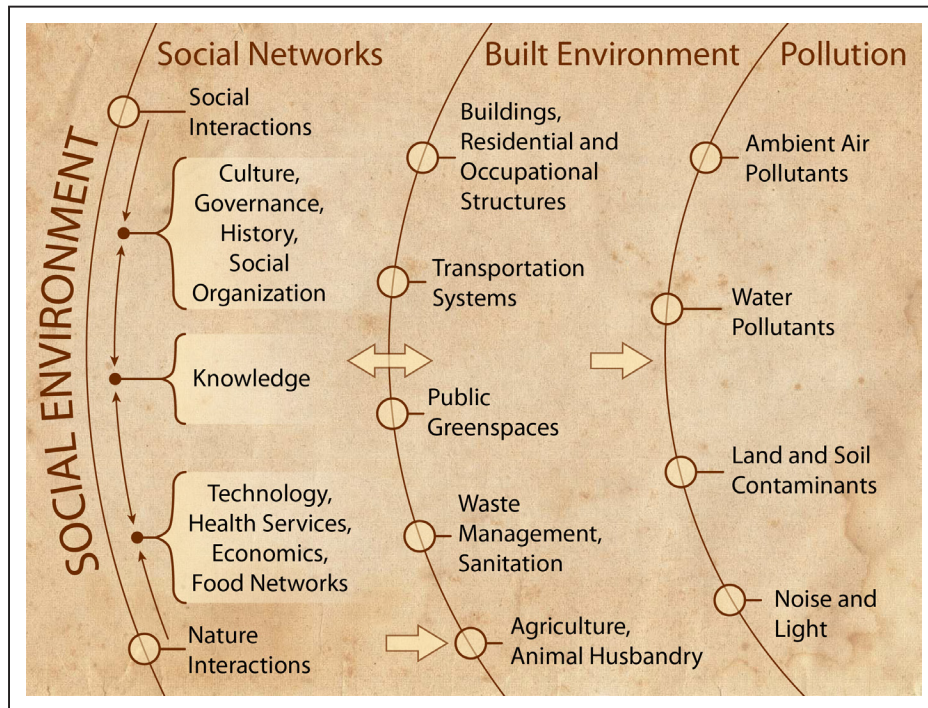


Figure 3. The social environment. Interactions of humans with nature and with each other results in the construction of social environments. Interactions with nature, such as agriculture or mining result in the development of technology, and lead to economic development, sustained by interactions between members of a society, which create elaborate social networks. Such networks are characterized by their distinct culture, history, governance, and organization. Interactions of humans with nature and with other members of society create knowledge and technology, which lead to the development of built environments. The built environment, in turn, supports increasing complex social networks and ensures preservation and transmission of knowledge and technology. Together, social networks and built environments are important determinants of cardiovascular health. They support health services and healthcare, and they enable specific behavioral choices. Social environments and the economic and interactive activities they support generate environmental pollutants that affect cardiovascular health. (Illustration credit: Ben Smith.)

and distribution. Humans depend on nature for food, whether through hunting or gathering or via agriculture, and social networks have been fashioned, in part, in response to this need. These networks are characterized by their interconnectedness, social support, inequality, and discrimination. Throughout human history, the social environment has played a cardinal role in human survival and health. Even now, differences in cultural systems may also be the single biggest barrier to the highest attainable standard of healthcare worldwide.⁴⁸ Cultural norms are important. They perpetuate, promote, or constrain health-related choices, and they moderate social responses to disease, healthcare, and mortality. An understanding of culture is therefore important, as culturally acceptable social organizations that give rise to poverty, oppression, and discrimination significantly affect cardiovascular health and disease susceptibility.

Social Networks

The importance of social networks is reflected by the enormous influence humans have on one another. CVD risk factors such as smoking and obesity form distinct clusters within social networks and spread through social ties,^{49,50} and the SES of an individual within a society has an important impact on health. Individuals with lower SES have poor health, and those with higher education consistently show better health. Although many health disparities have been linked to individual-level SES, neighborhood-level SES also plays a substantial role in individual health. For example, low SES residents

living in high SES neighborhoods have higher rates of mortality than those of the same SES who live in an area of comparable SES.⁵¹ In a remarkable study of 270 000 Bell employees in the United States, Hinkle et al,⁵² found that men who entered the organization with a college degree had a lower incidence and death rate from CHD. Factors that contribute to CVD risk associated with low SES remain to be fully identified, but may relate in part to a higher burden of classical CVD risk factors, as an individual's SES bears a strong inverse relationship with hypertension, smoking, obesity, and diabetes mellitus.⁵³ However, SES also seems to affect CVD risk independent of risk factors. For instance, in the Whitehall study men of the lowest SES had 2.7× the 10-year CHD death risk than those in the highest grade of SES.⁵⁴ After adjusting for classical risk factors, the relative risk was reduced to only 2.1, suggesting that at best, conventional risk factors seem to account only partially for the CVD risk imposed by SES. Clearly, other unappreciated environmental factors are at work. Indeed, it seems likely that some of the effects of SES may be because of the unique structuring, civic architecture, and characteristics of disadvantaged neighborhoods, particularly in the United States and other industrialized countries. By creating varying degrees of security and prestige hierarchies, SES produces its own culture that cuts across national and ethnic backgrounds,⁴⁸ to affect health in ways not yet understood.

Often independent of SES, characteristics of social networks such as oppression, safety, trust in institutions, impacts of

relationships of power, and prestige affect cardiovascular health. Multiethnic social networks, with their inherent tensions because of discrimination, oppression, and disparities, could create social hierarchies, uncondusive to cardiovascular health. Several studies suggest that Blacks in the United States who experience racial discrimination may be at heightened risk for CVD.^{55–57} There is a similar association between unfair treatment and subclinical CVD in White women.⁵⁸ Racial discrimination is also related to lower medication adherence, as well as a lack of trust in physicians.⁵⁹ Mechanisms underlying the link between discrimination and CVD risk remain unclear, but several, though not all studies, report that associations between perceived racial discrimination and hypertension,⁶⁰ which are stronger for institutional, rather than individual-level racism,⁶¹ and may be related to anticipatory stress or racism-related vigilance.⁶² However, the effects of structural (network-wide) discrimination is moderated by group cohesion, racial identity, social support, and individual coping mechanisms.^{63,64} Hence a comprehensive, omics approach is required to integrate different characteristics of social networks related to social deprivation, SES, discrimination, and hierarchy to develop a coherent understanding of their combined influence on cardiovascular health. The explanatory prowess of such models could be enhanced by adopting a life course approach as exposure to adverse features of social networks could have a greater effect at specific life stages or could have a cumulative effect during a life course. There is substantial evidence showing that childhood adversity (such as household dysfunction, bullying, exposure to crime, victimization, physical and sexual abuse, and economic disadvantage) is robustly associated with the risk for both—CVD and type 2 diabetes (T2D).⁶⁵ Racial and ethnic minority children living in low SES households, in particular, have higher childhood adversities, and as a result they experience higher prevalence of cardiometabolic disease across life course,⁶⁵ in part, because of the perpetuation of low SES leading to poor educational resources and few economic opportunities.

Built Environment

To sustain social networks, humans create artificial built environments. Since the beginning of civilization, settlement into cohesive communities of purposefully built environments has offered many advantages. Creation of houses and dwellings protected humans from elements of nature and ensured comfort and safety, which were particularly important for safeguarding human infants who have a protracted childhood. Later with the development of advanced cultures, the artificial, constructed environments consisting of public buildings, roads, and bridges helped promote commerce, social interactions, as well as the acquisition and protection of personal and public economic resources. In recent years, with the development of well-planned, sanitary cities, the rates of communicable diseases have plummeted worldwide. Nevertheless, the development of increasingly complex built environments has led to the progressive separation of humans from their natural ecosystems. Today, >50% of the world's population lives in highly structured built environments of cities and towns. The National Human Activity Pattern Survey shows that in the United States, 80% of the population lives in an urban setting, and spends 87% of their time indoors, and 6% of their time in enclosed vehicles.⁶⁶ As a result, the amount of time spent outdoors in a natural environment may be as low as 1%. Because of

this shift, most contacts of modern humans with the environment are limited to the built environment, and therefore, features and aspects of the built environment have become the primary determinants of human health, safety, and well-being. This has made it increasingly important to study and understand how aspects of the built environment affect human health.

The built environment includes all human-made physical parts of the envirome that provide living, working, and recreational spaces. It includes buildings, infrastructure, and machinery, including roads, bridges, parks, and transportation systems as well as distribution systems for water, electricity, food, etc. Although making buildings and settlements have been the hallmark of earliest humans, the accumulation of manufactured capital has been accelerating since the industrial revolution. Current estimates suggest that >800 billion tons of natural resources are stored in the built environment.⁶⁷ Such material stocks not only consume energy, generate greenhouse gases, and codetermine the amounts of waste and pollutants produced, they also affect human health and the risk of infectious and chronic diseases, particularly CVD, obesity, and T2D. Features of the built environment that are conducive to walking, cycling, etc, promote physical activity and thereby diminish the risk of obesity, diabetes mellitus, and CVD (Scheme). For instance, in the MESA study (Multi-Ethnic Study of Atherosclerosis), a 10 point (out of 100) increase in the score of walkability factors of distance to health-related locations and street network characteristics was significantly associated with a 16 minutes increase in transport walking, 11% odds of meeting walking goals and a 0.06 U reduction in body mass index.⁶⁸ In addition, features of the built environment—urban greenspaces, such as parks, street trees, and gardens provide a range of ecosystem services that benefit human health by promoting interactions with nature. The type of building as well aspects of buildings, such as age, materials used, number of windows, and number of levels, can also differentially affect the way in which humans interact with the built environment. Moreover, human health could be affected by how the physical components of the built environment relate to each other, in their location, density, and connectivity (land use). Nearby public buildings and visual landmarks provide a sense of ease and assist people in reaching their destination. In comparison, the density of fast food restaurants and liquor stores can negatively influence health⁶⁹ by promoting poor nutritional choices (Scheme). The local food environment plays an important role in the ability of residents to make healthy food choices, often intensifying health disparities in low SES areas. For example, low-income areas have been found to contain only 75% of the supermarkets as middle-income neighborhoods, with substantially fewer found in predominantly Black (52%) and Hispanic (32%) neighborhoods. The lack of fresh food in some neighborhoods forces its residents to visit retail stores with fewer healthy options⁷⁰; thereby, limiting healthy nutritional choices. The quality of life and population health is also affected by the connectivity of surroundings through transportation systems, including the infrastructure of roads, sidewalks, railroad tracks, bike paths, as well as traffic levels, bus, and subway systems. Inadequate infrastructure resulting in a lack of clean water and energy supplies, or mismanagement of toxic waste could lead not only to the transmission of infectious disease but increased risk of noncommunicable diseases as well.

In addition to the relational aspect of the built environment, the quality of surroundings, such as general attractiveness and perception of safety, can affect health by promoting greater physical activity, mental health, and social interaction. Living in deprived neighborhoods is associated with increased CHD prevalence and increased levels of CVD risk factors.^{71,72} Residents of disadvantaged neighborhoods have higher incidence of CHD, even after controlling for personal income, education, and occupation, or adjusting for established CVD risk factors.⁷² Aggregate results of >40 studies support the view that independent of individual SES, CVD risk is affected by neighborhood characteristics such as the availability and types of foods available, the publicity and availability of cigarettes and alcohol, the distribution of recreational spaces, transportation, and access to health and human services.⁷³ The impact of neighborhood characteristics may be further exaggerated by residential segregation. Racial/ethnic segregation in the MESA cohort has been found to be associated with increased CVD risk for blacks, but a decreased risk for whites.⁷⁴ Clearly, the CVD risk associated with residential neighborhoods may be related to experiential factors such as affective experience (attachment, sense of community), cognitive experience (satisfaction with neighborhood), and relational experience (social integration, social support, and stressful interactions),⁷³ important dimensions that should be accounted for in any comprehensive evaluation of the built environment and its impact on cardiovascular health.

Pollution

An important outcome of modern built environments is pollution, defined as unwanted, often dangerous material introduced into the natural environment that threatens human health and harms the natural ecosystem. Recent global estimates indicate that pollution is the largest environmental cause of disease and premature mortality. Worldwide pollution has been linked to > 9 million premature deaths (16% of all deaths worldwide), 3× more deaths than from AIDS, tuberculosis, and malaria combined and 15× more than from all wars and other forms of violence.⁷⁵ Although pollution leads to many different health outcomes, CVD, inclusive of stroke, is the number one cause of air pollution-induced premature mortality. Indeed, CVD is the leading cause of death, not only by air pollution but by any adverse environmental exposure. The World Health Organization estimates that most deaths because of environmental causes are because of CVD, which accounts for 4.8 million such deaths worldwide per year, whereas cancer or respiratory diseases because of exposure to adverse environments account for 1.7 and 1.9 million such deaths each year, suggesting that adverse environmental exposures are more likely to heighten the risk of CVD than any other health outcome.

Both urban and rural areas face pollution from many sources, including land, water, and air. Exposures to land pollutants—pesticides, and agricultural products are frequent and have been linked to exaggerated CVD risk. Exposure to chemicals, such as trichloroethylene, at large (Superfund) waste sites has been found to be associated increased incidence of insulin resistance and diabetes mellitus, and several volatile organic compounds generated in industrial waste such as formaldehyde, butadiene, and acrolein have been found to affect cardiovascular function and promote CVD.⁷⁶ The most pervasive exposure, of course, is ambient air pollution, consisting mostly of criteria pollutants such as PM, ozone,

as well as nitrogen and sulfur oxides. Extensive work has shown that exposure to particulate air pollution is associated with premature cardiovascular mortality. Acute exposure to fine PM (<2.5 µm in aerodynamic diameter; PM_{2.5}) has been linked to adverse cardiovascular events such as MI, stroke, cardiac arrhythmias, and sudden cardiac death, whereas chronic exposures are associated with increased burden of CVD risk factors, and accelerated the progression of atherosclerotic disease.^{77,78} In addition, there is significant evidence to suggest that metals such as cadmium and lead, and metalloids such as arsenic affect the development and the progression of CVD.^{76,78} Exposure to such pollutants is associated with changes in blood pressure, lipid metabolism, atherogenesis, as well as endothelial damage and dysfunction.⁷⁷ For instance, exposure to arsenic from drinking water has been associated with the development of CHD as well as electrophysiological abnormalities predictive of sudden cardiac death.⁷⁸ Similarly, exposure to lead has been linked to hypertension, and exposure to cadmium, a byproduct of mining and smelting, is associated with increased incidence of CVD, CHD, stroke, and heart failure.⁷⁸

In addition to chemical pollution, exposure to noise pollution could also be hazardous to cardiovascular health. Many studies have shown that constant exposure to noise can increase blood pressure, heart rate, and cardiac output, leading to an increase in CHD risk as well as stroke.⁹ Like noise pollution, light pollution could also affect CVD by disrupting circadian rhythms. For example, residence in areas with more nighttime lights is associated with elevated blood pressure, elevated pulse pressure as well as lower flow-mediated dilation.⁷⁹ However, the link between light pollution and the risk for CVD, T2D, or obesity has not been extensively studied.

Collectively, extant evidence supports the view that several aspects of the social environment strongly influence cardiovascular health; however, there has been little or no attempt to integrate these influences or to develop a more holistic, omics understanding of such social determinants of health.

Personal Environment

Nested within the social environment are individualized personal environments. These environments are created by an individual's living conditions and characterized by choices related to occupation, diet, nutrition, physical activity, and chemical use. Although lifestyle choices are sometimes considered behavioral, rather than environmental, they reflect the ways in which individuals relate to their environment, and therefore could be thought of as characteristics of the personal environment. Just as social environments reflect the collective mode of interaction of the society among its members and with nature, personal environments are modes of interaction of an individual with society and nature. Though unique, personal environments are constructed within larger social networks and shared with other individuals in the network; and therefore, nested within the social environment.

The domain of the personal environment is the most proximal to an individual (Figure 4), and it has 2 main characteristics that distinguish it from natural and social environments. First is a difference in scale. Although natural and social environments are larger domains of the environment (the ecosystem or the society), personal environments are microenvironments around an individual. Social, cultural, political, and economic

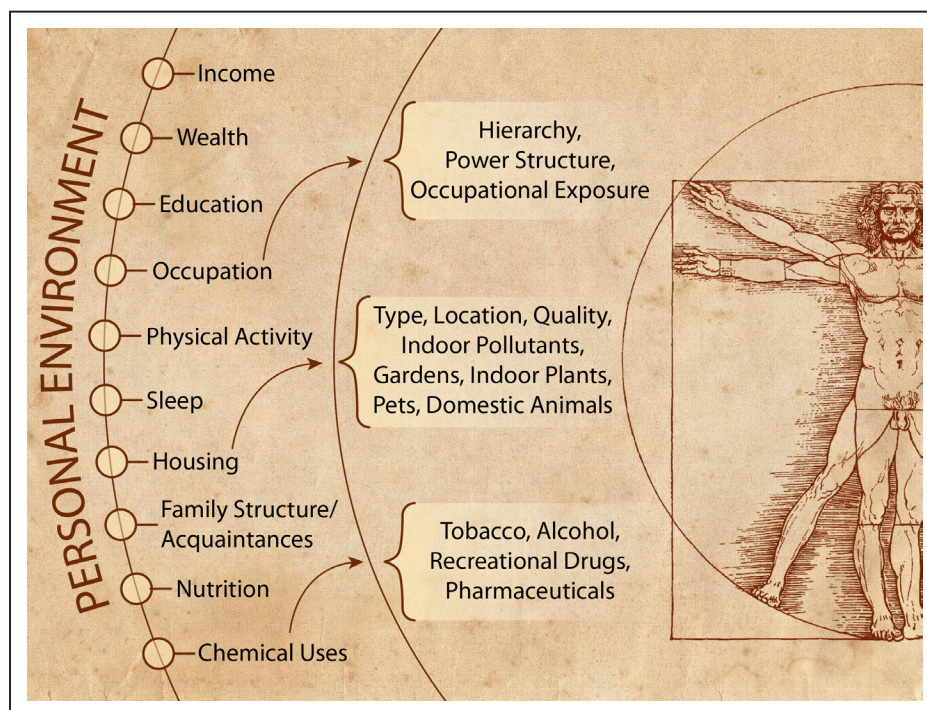


Figure 4. The personal environment. Personal microenvironments are created by either choice or chance. They are characterized by physical living conditions within a society, as well as smaller social networks comprised of family, coworkers, and immediate acquaintances. Each of these influence cardiovascular health and disease risk, as do personal income, wealth, and education. Components of both the natural and the social environments affect the creating and transmission of personal environments and shape lifestyle choices such as physical activity, sleep, nutrition, smoking, and the use of recreational drugs. (Illustration credit: Ben Smith.)

structures within a society are scaled down to immediate family and personal acquaintances, individual income, wealth, education, and occupation. Similarly, features that populate the biosphere—plants, animals, and microorganisms—permeate the personal environment, albeit on a smaller scale, as residential gardens, indoor plants, domesticated animals, or pets.

Lifestyle Choices

Another distinguishing feature of the personal environment is the element of choice. Even though constrained by the social environment, individual choices make up personal environments. In previous literature, these have been referred to lifestyle choices. These include important health determining choices such as nutrition, physical activity and the use of alcohol, recreational drugs, or tobacco. Because exposures caused by lifestyle choices are not entirely passive, they are sometimes not considered to be environmental factors (lifestyle choices; however, are included in the exposome).²¹ Nevertheless, consistent with the definition of the environment as anything external to the individual, not determined by genetics, lifestyle issues are part of personal environments. However, such choices are codetermined by the social and natural environments. For example, the density of fast food restaurants in a neighborhood has been found to be associated with rates of individual obesity⁶⁹ and that the number of tobacco shops in a neighborhood is reflective of smoking rates within the area,⁸⁰ suggesting that greater access to these products affects an individuals' choice to consume them. Differences in lifestyle choices may be related also to marketing, which often targets minority population. Several studies have shown

that such marketing is effective; for instance, it significantly influences children's food preferences as well as the type and amount of foods they eat.⁸¹ Findings of such studies suggest that the social environment has a strong influence on personal choices. Many lifestyle choices could be traced backed to (or modified by) elements of the social environment, such as business interests, regulatory policies, social and cultural forces, propaganda and advertisements, and recently, dark marketing, which targets specific audiences via the internet and social media. Hence, lifestyle choices cannot be considered in isolation as individual behavioral issues as they are nested within a larger social context. Nonetheless, some elements of the personal environments may be because of chance alone. In most societies, a person's birth circumstances are key determinants of their life course and children born to parents of low SES have more limited choices that children of high SES parents.

The significance of the personal environment as a key determinant of cardiovascular health is underscored by the role of lifestyle choices related to nutrition. In the Nurses' Health Study,⁸² replacement of just 5% energy from saturated to unsaturated fat was reported to be associated with a 42% reduction in CVD risk. And as shown by the PREDIMED trial (Prevention con Dieta Mediterranea), adherence to a Mediterranean diet supplemented with oils and nuts reduced the incidence of major cardiovascular events by 30%.⁸³ In global burden of disease estimates, poor nutrition and the lack of adequate intake of fruits and vegetable are some of the leading cause of death worldwide.⁸⁴ Hence, it has become increasingly important to understand how nutritional choices are determined; and how culture,

global markets, food networks, and retail food stores affect individual nutritional choices. A similar case could be made for physical activity. Although physical activity could be attributed to individual choice, recent work suggests that aspects of the built environment, such as access to local parks, greenspaces, and bike lanes can significantly influence physical activity in individuals living within urban communities.⁸⁵ Clearly, additional studies are required to define the components of the personal environment, to understand how these environments are created, and how specific factors in the social environments contribute to the composition and the development of an individual's personal environment within that society.

Domain-Specific Inquiry of the Envirome

The categorically-differentiated, domain-specific model of the envirome presented in Figure 1, could be useful in assessing the individual and integrated contributions of each of these domains to a person's health. Because each domain of the envirome (natural, social, and personal) can be described by components of similar characteristics, data from comparable databases could be used to define each domain by itself before studying how its effects are modified by other domains. Hence, the basic model of the envirome presented here could be developed iteratively into more complex models to include additional elements and relationships that might have been missed or overlooked here. Nonetheless, even in its rudimentary form, the current model has explanatory and predictive potential. It can explain how different domains affect each other and predict potential interactions, not only between different components of a domain but also between different domains. The model could also provide a framework for formulating new investigative questions and developing new research programs. The nested organization of the model could be used to explain how and why the influence of the natural environment is moderated by elements of the social environment, and how personal environments are constructed from surrounding social environments. It can explain, for example, why some elements of the built environment are what they are (because they fulfill overarching needs of social networks, eg, economic activity); why built environments or health and human services in some societies are less developed than others (because they reflect the knowledge, technology, and economic activity within that society); and why some individuals are more physically active than others (because they live in environments that are more conducive to physical activity). Importantly, the model aids in not only providing a useful understanding of the relationships between different domains of the environment, but it could also facilitate numeric and qualitative assessment of the integrative influence of the environment on cardiovascular health.

The model could be a blueprint or a roadmap for developing a more comprehensive understanding of environmental factors by prompting consideration of all 3 environmental domains for each environmental exposure studied. For instance, in studying the effects of ambient air pollutants guided by the model, we could ask how the surrounding natural environments affect the levels and chemical composition of ambient air pollutants; and how sunlight, plants, meteorology, geography affect formation, and dispersion of ambient pollutants. We could also examine how exposure to pollutants is modified by components of the built environment (roads, urban greenspaces); how the effects of

air pollutants modified by other copollutants (noise, light); and which characteristics of the personal environment (housing, nutrition, physical activity, smoking, sleep, chemical use, occupation, income, and education level) affect individual vulnerability to ambient air pollutant exposure. Some of these relationships are known. For instance, we know that smoking modifies the effects of ambient air particles,⁸⁶ and that the effects of smoking are modified by exposure to ambient PM⁸⁷; however, the effects of other social and environmental factors remain unknown and could be explored with the aid of the model.

Evaluation of domain-specific impact on each individual environmental factor could result in a more systematic and comprehensive analysis of the envirome than has been heretofore undertaken. Again, in case of studies on pollution, the model could assist in developing a pollutome to assess all major types and sources of exposure. A model of the pollutome has been previously presented to define the totality of all forms of pollution that has the potential to harm human health.⁷⁵ In this view, the pollutome encompasses all exposures during all stages of life and could be divided into distinct zones, depending on the extent of knowledge about the health effects of individual pollutants. The model succeeds in describing the current state of human knowledge about the health effects of pollution, but does not have a natural, source-oriented classification. Nor does it account for organic relationships of pollutants with health risk or relate them to other categories of the envirome. As shown in Figure 5, sources of pollution could be linked to different domains of the environment. Sources like volcanoes, forest fires, etc, could be mapped to the natural environment, whereas others such as agriculture, power generation, and biomass burning assigned to the social environment. Likewise, indoor pollutants could be located within personal environments. With such categorical differentiation, major pollutants could be linked to their sources and localized to specific parts of the geosphere (air, water soil) as well as specific domains of the envirome. Such categorization and differentiation may be helpful not only in identifying the location and the links between pollutants and their sources, but also in developing a comprehensive, omics assessment of pollutant exposures at both population and individual levels.

Considering all 3 domains of the environment could also guide a more comprehensive evaluation of lifestyle choices that affect cardiovascular health. For instance, even though nutrition is a personal choice (a component of the personal environment), the model could be used to ask how this choice is affected by features of the social environment such as the built environment, local availability of fresh foods, local agriculture and animal husbandry practices, food distribution networks, and economic and business interests in the region. More uniquely, we could ask: how knowledge of nutrition and technologies for food production and storage affect nutritional choices; how these choices are affected by culture, family structure, income and education; and how the effects of different foods are affected by local climate and geography (components of the natural environment). Similarly, we could ask how an individual's choice of physical activity and its effect on cardiovascular health are affected by other components of the personal (sleep, housing, nutrition, chemical use, wealth, and education), social (transportation systems, built environment, pollutant exposure, public greenspaces, and culture) and natural (climate, sunlight

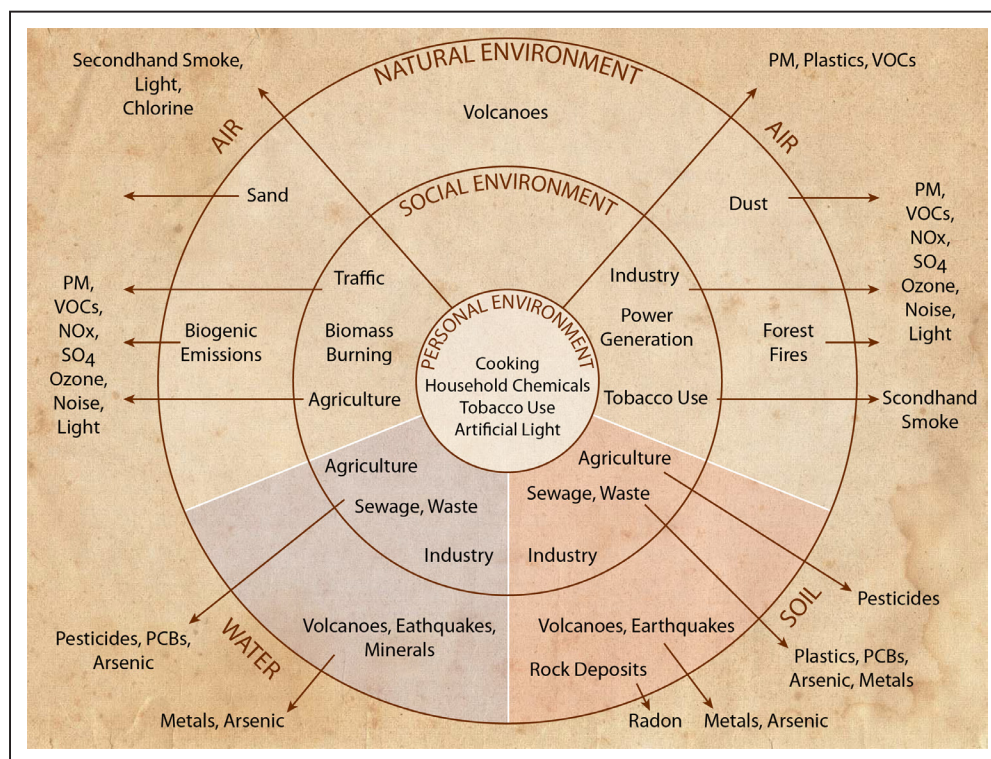


Figure 5. The human pollutome. Elements of each domain of the envirome are sources of air, water, and soil pollution. In the natural environment, events such as earthquakes, volcanoes, and forest fires can be a source of sporadic pollution either by emitting toxic gases and particles in the air and water or uncovering mercury and arsenic in the soil. Activities within the social environment such as agriculture, power generation, traffic, and biomass burning generate a variety of gaseous and particulate pollution, as well as noise and light pollution. Exposure to ambient pollutants within social environments could be moderated by characteristics of the personal environment, which in turn can be a source of additional exposure to particles and chemicals derived from cooking, the use of candles, incense, and cleaners. To define pollutant exposure as a whole, it is important not only to quantify pollutants in each environmental domain but also to account also for change or moderation of exposure from sources in one domain by another. It is also important to identify how characteristics of each domain modify exposure to pollutants in that and other domains. (Illustration credit: Ben Smith.)

exposure, geography, and meteorology) domains of the environment. Given the importance of personal environments in the analysis of CVD risk, it may be useful to start with lifestyle choices and then work backward to ask how these are affected first by the social and then by the natural environment.

Domain-wide evaluation of environmental influences could also provide new avenues for CVD control and prevention. Knowing which components of the social and natural environment affect individual choices of physical activity, drug use, nutrition, etc, and the extent to which these choices depend on other domains of the environment could help us develop more effective prevention strategies, by appropriate regulation and policy changes. For instance, rather than relying solely on personal motivation and education for encouraging physical activity and smoking cessation, we could promote changes in social and economic factors that support such activities. For example, in addition to individual counseling, population smoking rates could be decreased more effectively by increasing the price of cigarettes, socially denormalizing smoking behavior, minimizing cigarette advertisement, and decreasing the number of cigarette outlets in a neighborhood. Similarly, good nutrition could be promoted by increasing the availability of fresh foods, regulating harmful food constituents, increasing the efficacy of food networks, and technologies for long-term food storage rather than just motivating

individuals to consume healthier foods. In other words, altering components of the natural and social environments could provide more widespread and enduring gains than focusing on changing individual behavior.

Measurement of the Envirome

For integrated omics evaluation, the complexity of the environment must be distilled into quantified variables that can account for the characteristics of each of the different environmental domains. Although it is relatively straightforward to quantify many domains of the natural environment from geographic, geologic, and meteorologic data (Online Table I) other domains such as the biosphere and social and personal environments are more difficult to quantify. However, recent developments in ecology and social science are providing new ways of quantifying environmental factors. The biosphere, for instance, has been characterized by species richness and ecosystem structures, which have been used to construct useful proxy variables for biodiversity quantification of local organisms.^{47,88} Plant life could be accounted for, in part, by satellite-derived variables such as the normalized difference vegetation index, which is a measure of photosynthetic activity.^{42,44} Other variables such as tree canopy and quality of greenspaces have been used also, but their association with health remains to be fully validated. Nonetheless, it is difficult to integrate the effects of many components of the

natural environment. Hence, an alternative approach may be to use ecoregions to define a set of geographic and meteorologic features around individual populations. Ecoregions are well-defined areas that are generally similar in the type, quality, and quantity of environmental resources. Identified by the analysis of the patterns and composition of biotic and abiotic phenomena, these regions could serve as spatial units useful for studying the cardiovascular effects of the natural environment.

Quantification of the influence of the social environment is even more difficult because there is little consensus on how to define and quantify complex social constructs such as culture and technological knowledge. Similar difficulties arise when quantifying the health effects of customs, moral values, or belief systems. Although several sources of data could be used to quantify the characteristics of social networks, built environments, and the extent of pollution (Online Table II), quantification of social pressures and societal position remain problematic. Recent work has made important strides in assessing these concepts in terms that can be placed in a larger environmental context. For example, for the analysis of data from the Jackson Heart Study, a multidimensional scale has been developed to account for interactive and additive facets of racism and discrimination.⁸⁹ This scale has been subsequently utilized in other assessments of discrimination on CVD.^{90,91} Similarly, geographic location, and racial segregation and isolation have been operationalized at the metropolitan and neighborhood scales in relation to adverse outcomes.⁹² In addition, independent of race, cumulative measures of adversity, particularly early in life, have been associated with risk of adverse health outcomes in later life.⁹³

In contrast to the social environment, the personal environment, by definition, requires individual-level data. These are typically obtained through questionnaires, although emerging technologies are allowing for more quantitative estimates. Nutrition status can be obtained through food diaries or clinical techniques such as the subjective global assessment of nutritional status.⁹⁴ Use of indoor air monitors can measure the levels of household pollution. Individuals' transportation habits and physical activity can be monitored through personal sensors and GPS. Biomarker measurements using mass spectrometry can measure exposures to harmful pollutants, as well as tobacco and drug use.

Technological Advances and Envirome Research

Omics research in biology has been significantly facilitated and accelerated by technological developments in gene sequencing, electrophoresis, and mass spectrometry. Much of omics work that has been accomplished in the past 3 decades would not have been possible without such technological advances. Likewise, recent technological advances in monitoring natural, social, and personal environments provide new opportunities for a more comprehensive assessment of the envirome than has been heretofore possible.⁹⁵ Large-scale assessments of the natural and built environments are now possible with satellite imagery, and new developments are likely to provide better assessments in unprecedented detail. For example, the NASA TEMPO satellite, which is currently in development will have the ability to assess a suite of harmful pollutants on an hourly basis with high spatial variability.⁹⁶ Unmanned drones, equipped with sensor payloads,

could also be used to monitor emissions and air quality with unprecedented spatio-temporal resolution.⁹⁷ The conjunction of detailed time/activity patterns and high spatio-temporal resolution monitoring of air pollutants will yield unprecedented access to key components of the envirome. The assessment of the personal environment is perhaps likely to benefit the most from technological advancements, such as handheld and wearable devices, which are capable of assessing geographic location, personal movement, real-time questionnaire responses.^{93,98} Devices, such as smart watches, can assess movements, sleep, and heart rate, with other sensors in development to measure other indicators in real time,⁹⁹ could provide a more comprehensive evaluation of the personal environment in future studies.

Despite such developments, implementation of the envirome approach to understanding CVD will require additional technological advances in high-dimensional characterization of biological systems in concert with high volumes of data derived from newly developed technologies to assess environmental domains and human time-activity patterns. Moving beyond the simplistic accounting of a limited set of variables will require new methods to characterize natural, biological, and social systems. Technological advances in omics fields offer guidance for integrating large multifaceted data sets to assess biological systems. Network-based multi-omics analyses are already being used in genomics and metabolomics to discover previously unknown links between many layers of complex biological systems¹⁰⁰—an approach that could also be applied to envirome research. Advances in artificial intelligence may offer another way to account for environmental influences and for understanding, linking, and processing complex systems beyond the scope of human capabilities, with the ultimate goal of development and implementation of effective public health policies.¹⁰¹ These new forms of analysis, applied to an envirome approach to disease, may yield novel information about the human–environment interface and fresh insights into CVD.

Omics Analysis of the Environment

With the domain-specific model of the envirome, the influence of the environment on cardiovascular health and disease risk could be analyzed using a modified version of current omics approaches. The analysis could begin by asking (1) how different environmental domains (personal, social, natural) are related to CVD, risk, progression, and events? (2) Which specific domains and interactions within each domain affect cardiovascular health in the context of the total envirome? And (3) how different domains of the envirome interact and affect each other? The ontology developed here could provide a starting point for such analysis. First, by defining the subdomains and hierarchy of the natural environment (biosphere, geosphere), social environment (social networks, built environment, pollution), and the personal environment (SES, nutrition, housing, physical activity, sleep, chemical use), we can begin to understand how these components are related. However, for this, high-quality data sources are needed to provide measurements of subdomains such as the built environment, socioeconomic factors, and pollution. With such data, we can begin to identify which metrics most accurately measure the environmental components of interest. Because these data are likely to be derived from various sources, qualities,

and formats, data integration is likely to play an important role in preparing for statistical analysis. Finally, because the envirome encompasses the totality of a person's environment, both past and present, a life course approach²² is needed to understand how and when specific environmental components influence cardiovascular health by studying the long-term effects on chronic disease risk of exposures during gestation, childhood, adolescence, young adulthood, and later adult life.¹⁰²

In addition to the exposome approach, there have been other attempts to study the effects of the environment integratively. For example, to assimilate multiple environmental factors, Messer et al¹⁰³ have developed an environmental quality index, which encompasses 4 specific elements: domain identification, data source acquisition, variable construction, and data reduction. Distinct indices for air, water, land, built, and sociodemographic factors were created to characterize each county within the United States. A similar approach could be used to analyze the cardiovascular effects of the envirome in one particular individual. Such a personal envirome index could combine variables based on the 3 environmental domains using data reduction techniques, which then can be used to identify the cardiovascular impact of the environment as a whole. Specifically, to construct a replicable process, we need first to identify the domains and subdomains of the envirome (Figures 2 through 4). Then, by grouping like components, we can create indices in the natural environment representing the biosphere and geosphere. Similarly, for the social environment, we can create indices describing the social network, built environment, and pollution; and finally, an individual characteristic index, representing the personal environment.

In addition to evaluating the relationship of the envirome as a whole on cardiovascular health, we can identify specific components that contribute to this relationship. For such an analysis, it may be important to determine how modifying factors, interactions, and hierarchy of the environmental domains influences cardiovascular health. However, this is possible, only when studying all of the components of the envirome collectively, and by distinguishing between direct and indirect effects of different domains and subdomains of the environment on an individual's cardiovascular health. Similar approaches have been developed for EWAS (Environment-Wide Association Studies)¹⁰⁴ to search for environmental factors associated with disease. This model uses methodology borrowed from GWAS, with the idea that multiple environmental factors (akin to different genes) may influence disease susceptibility in a systematic fashion. The approach is advantageous as it uses all evaluated environmental factors, which limits the number of false-positive findings. However, the application of this approach has been limited. Patel et al,¹⁰⁴ for example, examined the associations between multiple environmental contaminants and T2D, while adjusting for lifestyle factors as confounders. However, based on the ontology developed in the current article, factors in the social and natural environmental environments that affect lifestyle choices could be included in such EWAS analysis. The EWAS procedure fits linear regression models independently for each covariate. The significance of each association between predictors and response is assessed and a multiple comparison correction, such as false discovery rate, is applied. Subsequently, significant covariates are included in a multiple linear regression model, with interactions,

to test for associations with the health outcome, while controlling for all significant environmental characteristics. Because of the high correlation, and numerous interactions between different components of the environment, there is growing interest in researching statistical methods that can address such issues.^{105,106}

Some alternative methods to EWAS include elastic net, sparse partial least squares regression, deletion/substitution/addition algorithm, and Group-Lasso INTERaction-NET. Because current statistical approaches required to analyze the complexity of the envirome may be suboptimal, additional approaches for the analysis of the envirome may need to be developed in the future.

The organizational view of the environment within each domain can be thought of as a complex web of interrelated and interconnected components. Having identified these components, the theories of network science can be tested and applied to environmental health problems with the goal of mapping environmental interactome networks. An environmental network map would comprehensively describe all possible environmental interactions related to CVD. Network science simplifies complex systems, by summarizing them as nodes (components) and edges (interactions) between them. In the environment, the nodes are components of the natural, social, or personal domains, whereas the edges are environmental, physical, and biological interactions, or alternatively correlations above a certain threshold. The resulting interactome can be mapped and used for modeling at the scale of the total environment. This will allow us to identify nodes (environmental components) of high importance, which could be the focus of future cardiovascular prevention strategies. Based on the structure of the network, the consequences of node removal would be drastically more beneficial than edge perturbation. Removing a node not only disables the effects of the node, but also the interactions associated with it. Although the removal of an edge would only remove one (or a few) interactions, leaving the node functioning, and would have a small improvement in CVD risk, if any. Studying the complete environmental network along with intervention strategies to potentially remove nodes and edges from the network could provide new clues into the mechanisms underlying CVD. In this regard, Bayesian network analysis may be particularly advantageous in studying environmental components based on the question at hand, as they are being increasingly used in ecosystem modeling.^{107,108} Although promising, additional work is required to assess the utility of Bayesian approaches for the analysis of the health effects of the envirome.

Perspective

Given that a majority of CVD is preventable and CVD risk is modifiable, understanding the role of the environment is critical for the development of future prevention and treatment strategies. To date, most prevention strategies have focused on the individual, however, an individual's actions are shaped by the surrounding environment, understood holistically as the envirome. An understanding of how different components of the envirome interact could influence both personal decisions and regulatory policies, for instance, by promoting modification of the built environment to create better access to nutrition, more walkable areas, and more public greenspaces. Although such lifestyle factors matter, modification of individual choices is not easy. As suggested by our model, changes in the personal environment depend on characteristics of social

networks such as the economics, social organization, knowledge, technology, local governance. Therefore, to change individual choices, it is important to examine the larger social and natural environments that shape such choices. Hence, to have the greatest impact on CVD prevention, it is essential to understand the totality of environmental influences. The model of the human envirome described here provides such a paradigm, which though new to environmental cardiology, could provide a better understanding of the causes of CVD and point to new ways of preventing them.

Nonetheless, many questions remain about the associations between CVD and the environment. The ontology of the current article, while not exhaustive, provides a starting point to address these complex questions. Studying the complete human envirome is a difficult undertaking, and a robust multidisciplinary program of scientific research is needed to generate evidence-based answers to these questions. Identifying and gathering the necessary data to capture all aspects of the environment will require both time and resources to address the complexity of environmental data from many, disparate sources. However, the development of innovative tools and analytic techniques in the omics fields and new tools for studying the environment and monitoring individual activities and exposures represent exciting opportunities for studying the human envirome. Results of such research could guide future interventions. Individuals from a wide range of disciplines including medicine, basic research, government, sociology, economics, urban planning, and ecology could use the envirome model to understand, prevent, and treat CVD and create healthier living environments.

Sources of Funding

This study was supported in part by grants from the National Institutes of Health (ES19217, ES023716, HL120163, HL120746, and HL55477).

Disclosures

None.

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